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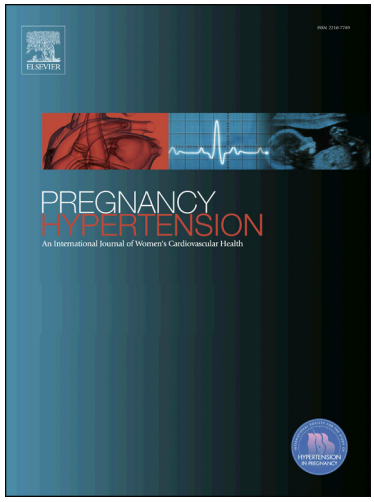

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Placental Growth Factor Informed Management of Suspected Pre-eclampsia or Fetal Growth Restriction: The MAPPLE Cohort Study

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Abstract

Objectives

Placental Growth Factor (PlGF) has been shown to be beneficial in diagnosing pre-eclampsia. We performed a prospective cohort study of revealed PlGF in standard clinical use in four teaching hospitals in UK, Germany, Austria and Australia.

Study Design

Clinical data from women with suspected pre-eclampsia or fetal growth restriction < 35 weeks' gestation with revealed PlGF measurement were collected (MAPPLE study).

Main Outcome Measures

Data were compared to the PELICAN study (PlGF concealed). Pre-specified outcomes were compared using standard statistical tests (median difference or Risk Ratio). The results were further categorised by PlGF concentration: i) very low (<12pg/ml), ii) low (12-100pg/ml), iii) normal (>100pg/ml).

Results

396 women managed with revealed PlGF (MAPPLE) were compared with 287 women with concealed PlGF (PELICAN). Revealed PlGF led to delivery 1.4 weeks earlier (-2.0 to -0.9, 34.9 weeks vs 36.7 weeks). There were no significant differences in maternal adverse outcomes (11.9% vs 10.1%, Risk Ratio (RR) 1.17, 95%CI 0.76-1.82) or caesarean sections (73.8% vs 64.5%; RR 1.14, 95%CI 1.03 to 1.26). Revealed PlGF led to fewer perinatal deaths (2 vs 9; RR 0.16, 95%CI 0.03 to 0.74) and fewer babies with birthweight <3rd centile (28.9% vs 36.1%; RR 0.80, (0.65 to 0.99), but with more neonatal adverse outcomes (30.4% vs 17.1%; RR 1.78, 95%CI 1.32 to 2.41).

Conclusions

Revealed PlGF may be associated with lower perinatal mortality and birthweight <3rd centile but appears to lead to earlier delivery with more neonatal respiratory morbidity. Randomised trials with adequate power for clinical outcomes are needed.

Funding

Financial assistance was received from Alere to support the running of the MAPPLE database. Alere had no access to the information or control over the database itself.

Keywords

Placental Growth Factor, Pre-eclampsia, Pregnancy Outcome, Small for Gestational Age Fetus, Stillbirth

Highlights

- We report PlGF-led management of pregnant women as part of routine clinical care
- We compared our revealed PlGF cohort to a previous cohort with concealed PlGF results
- Revealed PlGF leads to earlier delivery by 1.4 weeks
- Revealed PlGF leads to fewer perinatal deaths and babies <3rd centile at birth
- Revealed PlGF increased neonatal morbidity, predominantly due to respiratory causes

Introduction

Pre-eclampsia is a multisystem disorder affecting 3-5% of pregnancies and is associated with abnormal placentation and placental dysfunction (1). The detection of pre-eclampsia is a major focus of maternity care as it remains a significant cause of maternal and perinatal morbidity and mortality (1). The only treatment for pre-eclampsia currently available is delivery and therefore accurate diagnosis with the aid of a biomarker could allow adjustment to clinical care.

Placental Growth Factor (PlGF) is one of several biomarkers which have been shown to have a predictive capacity for the screening and detection of pre-eclampsia (2, 3). PlGF is produced by the syncytiotrophoblast and is identifiable in maternal blood from as early as 12 weeks (4) with concentrations increasing with gestation until around 30 weeks before declining until birth (5). A decline in PlGF appears to represent a negative syncytiotrophoblast stress response to a variety of insults ranging from hypoxia (6), inflammation, oxidative stress(7) and is as such also seen as part of syncytiotrophoblast aging. PlGF concentrations are lower in pre-eclampsia (2), and extremely low in severe early-onset pre-eclampsia (8). Recently it has also been suggested that low PlGF concentrations are associated with fetal growth restriction (FGR) (9) and placental dysfunction (10).

Currently the National Institute for Health and Care Excellence (NICE) (11) recommends the use of two platforms for PlGF assessment in pregnancy, produced by Alere (2) and Roche (12). The Alere platform uses antibodies against PlGF isoform-1, with some cross-reactivity for isoform-2, and has a moderate body of evidence for its clinical effectiveness at determining pre-eclampsia requiring delivery within 14 days (PELICAN study) (2, 13). The Roche platform, which measures soluble FMS-like tyrosine kinase-1 (sFlt-1) relative to PlGF also has a developing body of evidence (PROGNOSIS study) (12). Both tests have been endorsed by NICE for the investigation of hypertension in pregnancy, to 'rule out' a diagnosis of pre-eclampsia (11). Economic benefits, with savings of approximately £500 per patient, have also been suggested to be achievable if a PlGF based management pathway for women with hypertension in pregnancy is instigated (13).

To date there have not been any published randomised controlled trials of the use of PlGF as a diagnostic test in women with hypertension in pregnancy. The best estimates of cost-effectiveness and clinical utility will come from randomised controlled trials such as the PARROT study (14). However, until these are available comparative cohort studies may offer an insight into the clinical impact of PlGF, when used as a diagnostic test in women presenting with suspected pre-eclampsia. The objective of the MAPPLE study was

to report clinical outcomes in women managed with revealed PlGF results and to compare those outcomes with those of the PELICAN study (2) in which clinicians were not informed of the PlGF result. This would identify the potential clinical implications of revealing PlGF results to the clinician.

Methods

The Management of pregnancy complications with PlGF testing (MAPPLE) registry was established as a prospective cohort of women managed with revealed PlGF results according to local guidelines as part of clinical service evaluation. Four maternity units agreed to compile data on women with pregnancies complicated by suspected pre-eclampsia or fetal growth restriction managed with revealed PlGF as part of standard maternity care and funded from within maternity budgets. Participating units were located in the United Kingdom (Liverpool), Austria (Salzburg), Germany (Osnabrück) and Australia (Adelaide).
A single 2.5ml whole blood sample was taken from each women into bottles containing ethylenediamine tetra-acetic acid. The plasma derived after centrifugation at 3000rpm for 5 mins was tested for PlGF concentration, using the Triage system (Alere, San Diego, CA), according to the manufacturer's instructions. All meters were programmed throughout to produce a revealed PlGF result available immediately to laboratory and clinical staff. The assay uses fluorescently labelled recombinant murine monoclonal antibodies targeted to PlGF, which provide a quantifiable result within the range 12 to 3000pg/mL, within approximately 15 minutes. The manufacturer states a limit of detection of 9-3000pg/ml (11).

Women presenting prior to 35 weeks' gestation attending their local hospital with suspected pre-eclampsia or fetal growth restriction were offered PlGF testing in line with local hospital policy. No consent was required as PlGF informed management constituted routine care in these units. Clinicians were aware of the PlGF result and were expected to adjust care accordingly. An example of the PlGF guideline used at Liverpool Women's Hospital can be found in Supplementary Text 1.

Anonymised clinical data were entered onto a dedicated study case report form. A data transfer agreement was in place at each site before uploading to a secure database (Simplified Clinical Data Systems, Portsmouth, NH). The uploaded data were assessed for completeness by the lead author. Ethical permission was not required as no identifiable patient data were used.

Data for clinical outcomes were compared, where possible, between revealed (MAPPLE) and concealed (PELICAN) cohorts (2) using median differences or risk ratios. Only the initial PlGF assessment was used even if more than one sample was taken to maintain consistency with the PELICAN study.

The study is essentially a comparison of two cohorts of pregnant women, selected under different circumstances and for different reasons. Accordingly, we decided to conduct an unadjusted comparison between the studies, which reported on all the important measures, and estimated the size of the differences and then to adjust comparisons for the principal differences between the women prior to PlGF testing. Adjustment was made for maternal age, BMI, nulliparity, and proteinuria. For the adjusted analysis, women with twin pregnancies were excluded, as were women where key predictors were missing. When comparing event rates (e.g. perinatal deaths, perinatal adverse outcomes, results were expressed as odds ratios, with 95% confidence intervals. For the main continuous measures birthweight and gestational age at delivery, differences in the mean were calculated. For additional measures, either means (with SD) or medians (with quartiles) were presented. Data are presented in the previously derived ranges of <12pg/ml (very low), 12-100pg/ml (low; representing <5th percentile of normal) and >100pg/ml (normal) (2, 10). Birthweights are presented as customised fetal weight centiles (15). We examined whether apparent differences in infant outcomes could be due to confounding at baseline (maternal age, singleton pregnancy, ethnicity, pre-gestational diabetes, APS/SLE, previous pregnancy complications, new hypertension, suspected FGR and proteinuria) using multiple regression. We also compared the unadjusted and adjusted impact of revealed PlGF on management of pregnant women (antenatal steroid use, induction of labour, Caesarean section) using an interaction test.

Results

Between April 2014 and March 2016, clinical outcomes were obtained from 396 women presenting prior to 35 weeks' gestation with a known PlGF result and complete outcome dataset. The clinical datasets included for analysis came from Liverpool: 241 women; Osnabrück: 115 women; Salzburg: 26 women; Adelaide 14 women.

The MAPPLE cohort varied from the PELICAN cohort in a number of demographic features (maternal age, twin status, ethnicity, pre-gestational diabetes, APS/SLE, and complications of previous pregnancies) as shown in Table 1. The distribution of PlGF sub-groups at first sampling were similar.

There were no significant differences in maternal adverse outcomes between women in the MAPPLE cohort compared to those in the PELICAN study (11.9% vs 10.1%, Risk Ratio 1.17; 95% confidence intervals 0.76 to 1.82) with the majority of complications related to hepatic and renal dysfunction (Table 2).

There were 433 babies in the MAPPLE cohort and 299 in PELICAN (Table 2). There was a single stillbirth within the MAPPLE cohort, in a woman with chronic hypertension with superimposed pre-eclampsia and

severe early-onset FGR who withdrew from clinical care before presenting two weeks later with an intrauterine fetal death. There were significantly fewer perinatal deaths in the MAPPLE cohort (n=2, 0.5%) compared to those in the PELICAN study (n=9; 3.0%; Odds Ratio 0.16 (0.03 to 0.74). More babies experienced a composite perinatal adverse outcome in MAPPLE (n=133, 30.7%) than in PELICAN (n=61; 20.4%; Risk Ratio 1.51 (1.15 to 1.98), Neonatal adverse outcomes were more common in the MAPPLE cohort (n=131; 30.4% vs. n=51; 17.1%; Risk Ratio 1.78 (1.32 to 2.41); these were dominated by respiratory morbidity including respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD). A higher proportion of babies in the MAPPLE cohort were admitted to the neonatal unit compared to those in the PELICAN study (n=190; 45.5% vs n=117; 39.8%; Risk Ratio 1.14 (0.95 to 1.37).

The time between first PlGF test and delivery was shorter when PlGF result was revealed to the clinician with a mean difference of 6 days (-2.0 to -10.0; 24 days vs 29 days) (Table 3). A greater proportion of women with revealed PlGF (n=236; 59.9%) received antenatal steroids for fetal lung maturation compared to PELICAN (n=88; 30.1%; Risk Ratio 1.95; 1.61-2.37).

Fewer women had fetal ultrasound assessment performed after PlGF sampling when PlGF was revealed (89.1% vs 98.7%; Risk ratio 0.90; 0.87 to 0.94) but the proportion of women with estimated fetal weight (EFW) <10th centile or abnormal fetal Doppler (absent or reversed end diastolic flow in the umbilical artery) was similar in both studies. There was no evidence of revealed PlGF testing affecting decisions to give steroids (p=0.09), induction of labour (0.13) or Caesarean section (0.18) assessed using interaction tests. Women with revealed PlGF results were delivered at an earlier gestation with a mean difference of 1.4 weeks (-2.0 to -0.9, 34.9 weeks vs 36.7 weeks). There was an increased likelihood of the fetus being delivered by caesarean section in the MAPPLE cohort compared to the PELICAN cohort (73.8% vs 64.5%: Risk Ratio 1.14, 1.03 to 1.26). In women managed with revealed PlGF results, there was a significantly lower risk of women delivering a small for gestational age (SGA) infant <3rd centile (Risk Ratio 0.80; 0.65 to 0.99) compared to those managed with concealed PlGF results.

Evaluation of principal outcomes in women with a singleton pregnancy (n=356 in MAPPLE; n=275 in PELICAN) with adjustment for baseline confounders did not substantially change the findings: mean gestation at delivery 34.4 (SD 3.6) vs. 36.0 (3.8) weeks; unadjusted median difference -1.33 (-1.89 to -0.77) and adjusted median difference -0.95 (-1.60 to -0.31) weeks; perinatal adverse outcomes 28.4% vs. 18.9%; uOR 1.74 (1.20 to 2.51) and aOR 1.51 (0.93 to 2.43). When analysis was restricted to singleton pregnancies, the increase in Caesarean sections was of borderline significance (uOR 1.39; 1.00 to 1.95) and the odds

reduced (and not significant) when adjusted for baseline confounders between the cohorts (aOR 1.33; 0.85 to 2.07).

Tables 4 and 5 report maternal and perinatal outcomes for women managed with revealed and concealed testing by PlGF sub-group (<12, 12-100 and >100pg/ml). A greater proportion of women in the very low PlGF group in both cohorts had maternal adverse outcomes (compared to the other groups) and the interval from sampling to delivery was shortest in this group. As these two cohorts are not from a randomised comparison, and the cohort has been further divided, further statistical testing has not been undertaken. All stillbirths and perinatal deaths in revealed and concealed cohorts occurred in singleton pregnancies with abnormal PlGF concentrations (low or very low) (Table 5). Gestation at delivery was earliest in women with lowest PlGF concentrations, whether the result was revealed or concealed.

Discussion

In women managed with revealed PlGF results, there were fewer perinatal deaths; this may be due to modifications in surveillance and monitoring of these pregnancies than if the PlGF result were unknown. Previous observational cohorts have demonstrated a correlation between low PlGF concentrations at 19-24 weeks' gestation and subsequent stillbirth (16). Whilst around 25% of fetuses in both cohorts were identified as having an estimated fetal weight <10th centile on ultrasound at presentation, there were significantly fewer infants born small for gestational age (<3rd centile) in those managed with revealed PlGF results, even after adjustment for baseline predictors, suggesting that earlier delivery due to revealed PlGF may have prevented a slowing of fetal growth in utero. Revealing PlGF was associated with a shorter diagnosis to delivery interval and an earlier gestation at delivery. We observed a similar rate of antenatal diagnosis of SGA as the 15% observed in the sFlt1:PlGF study by Zeisler et al. (12).

The revealing of PLGF to the clinical team was associated with a significant reduction in perinatal mortality. Not surprisingly this gain comes at the cost of increased neonatal unit admissions and perinatal morbidity, in particular respiratory complications. This higher prevalence of respiratory morbidity in the MAPPLE cohort may be related to the earlier gestation at delivery or increased use of caesarean delivery and was not ameliorated by an increased use of antenatal steroids. Diagnosis of respiratory distress syndrome and bronchopulmonary dysplasia was similar across centres within the MAPPLE study; it was higher than that in the PELICAN study and the 10% observed in the TRUFFLE cohort of growth restricted fetuses (who share many features with women in the PlGF <12pg/ml subgroup) (17).

Around 10% of women in both cohorts had maternal adverse outcomes, similar to previous observations (2), with the majority of adverse outcomes other than abnormal biochemistry in women with very low PlGF concentrations. There was less preeclampsia in the revealed cohort perhaps suggesting that earlier intervention prevented a worsening of the maternal condition. However, women managed with revealed PlGF results required frequent attendance at antenatal clinic and admission, possibly due to the persistence of hypertension and other risk factors.

This is the largest cohort study to date assessing the impact of PlGF informed care on pregnancy outcome and provides generalisable 'real life' data applicable across healthcare systems. At present these data provide the best information about the consequences of PlGF results in pregnancy. Outcomes have been compared between women managed with revealed results (MAPPLE) and those managed with concealed results (PELICAN) and variation in practice, differences in multiple pregnancy numbers or ethnicity between different countries could influence some of the outcomes. Statistical comparison was limited to those least influenced by possible variations in practice.

Our findings are confirmed by the much smaller study by Cetin et al. (18), which assessed just 57 women with pre-eclampsia and 16 with fetal growth restriction.

Conclusion

Implication for practice

Our data demonstrate that PlGF-informed management of high-risk pregnancies is feasible within standard clinical care. This study was not designed to demonstrate cost-effectiveness or perform an economic analysis of the use of PlGF, but previous assessments have suggested cost savings with PlGF use. Overall, our study suggests that early intervention with PlGF-led management may prevent worsening of fetal health but at the expense of earlier delivery and increased neonatal complications, almost exclusively due to respiratory morbidity, despite increased use of antenatal steroids. This may be offset by lower perinatal mortality and fewer small for gestational age babies.

The statistically significant reduction in stillbirths between revealed and concealed PlGF led care is of interest but there should be caution in interpreting these data in light of the methodological differences between these two cohorts. Further evidence from randomised controlled trials will assist in interpretation of these findings. However, studies powered for stillbirth and perinatal death as an outcome are difficult to perform. The pattern of earlier delivery suggests that clinicians consider optimal management and timing of delivery in response to the knowledge of PlGF. However, earlier delivery (by six days) was also associated with

worsened short-term neonatal outcomes; this may have been influenced by a lower gestation at enrolment in the revealed cohort and by the overall earlier gestation at delivery of 1.4 weeks. Education of obstetric teams and increased confidence in PlGF assessment over time to ensure that PlGF use leads to increased surveillance rather than precipitating delivery may optimise the benefit (i.e. reduced perinatal death) while limiting iatrogenic delivery. Likewise, the mode of delivery should be determined by accepted obstetrical indications rather than PlGF result alone. This should be considered when planning to introduce a new tests in a high risk population.

Implications for research

The nature of this study, with different cohorts, precludes more detailed interpretation of the results in table 4 and 5. The true picture of potential clinical benefit or harm from PlGF-led management will only come from further randomised studies of its use as well as full cost-effectiveness assessment. Until the results of these studies are available, caution should be exercised before moving to PlGF-led management for all high-risk women. Ongoing and future randomised studies should have adequate power to confirm or refute our findings.

Disclosure of Interests

A Sharp and Z Alfirevic received financial assistance from Alere to support the running of the MAPPLE database. Alere had no access to the information or control over the database itself.

A Shennan has been paid as a consultant for and received honoraria from Alere and has also been paid as a consultant for Roche and Perkin Elmer.

All other authors declare no conflict of interests.

Contribution to authorship

A Sharp and ZA conceived the idea and performed the analysis and wrote the manuscript. LC and A Shennan provided data from the PELICAN study and wrote the manuscript. PS performed statistical analysis. TF, KH, SP, ZO, YG, MT and GD all provided data and reviewed the manuscript.

Ethics approval

Ethical permission was not required as no identifiable patient data were used.

Funding

This study was funded by financial assistance from Alere to support the running of the MAPPLE database. Alere had no access to the information or control over the database itself.

Table 1: Demographic data and clinical characteristics at enrolment for women in MAPPLE (revealed PlGF testing) and PELICAN (concealed PlGF testing) cohort studies presenting prior to 35 weeks' gestation.

	MAPPLE (revealed PlGF testing)	PELICAN (concealed PlGF testing)	Risk Ratio
	n=396	**n=287**	
Age (years; median, quartiles)	31 (27-35)	32 (27-36)	-1.3 (-0.4 to -2.3)
BMI (kg/m2; median, quartiles)	27 (24-32)	29 (24-34)	-0.8 (-0.1 to -1.8)
Nulliparous	208 (52.7)	164 (57.1)	0.92 (0.80 to 1.06)
Singleton pregnancy	360 (90.9)	275 (95.8)	0.95 (0.91 to 0.99)
Current Smoking	43 (11.3)	24 (8.6)	1.32 (0.82 to 2.12)
Ethnicity: White	357 (91.1%)	187 (65.6%)	
Ethnicity: Black	12 (3.1%)	70 (24.6%)	0.12 (0.07 to 0.22)
Ethnicity: Asian	8 (2.0%)	19 (6.7%)	0.24 (0.11 to 0.53)
Ethnicity: Other	19 (4.8%)	11 (3.8%)	
Previous Medical History			
Previous Preeclampsia	87 (22.0)	55 (19.2)	1.15 (0.85 to 1.55)
Chronic Hypertension	55 (14.4)	45 (15.7)	0.83 (0.58 to 1.19)
Systemic Lupus Erythematosus/ Antiphospholipid syndrome	6 (1.5)	12 (4.2)	0.34 (0.13 to 0.89)
Pre-gestational diabetes	37 (9.3)	6 (2.2)	4.19 (1.79 to 9.79)
Renal Disease	14 (3.5)	19 (6.6)	0.50 (0.26 to 0.98)
Previous hypertensive disorder of pregnancy (excluding preeclampsia	7 (1.8)	15 (5.6)	0.32 (0.13 to 0.77)
Indication for PlGF testing (non-exclusive)			
New onset of hypertension	314 (79.5)	155 (54.0)	1.47 (1.31 to 1.66)
Persistent epigastric/ right upper quadrant pain	12 (3.0)	18 (6.3)	0.48 (0.24 to 0.99)
Suspected fetal growth restriction	66 (16.7)	25 (8.7)	1.92 (1.24 to 2.96)
Proteinuria	59 (14.9)	161 (56.1)	0.27 (0.21 to 0.34)
Gestational age at sampling, (weeks; median, quartiles)	30.7 (27.7-33.1)	31.0 (27.9-33.4)	-0.1 (0.3 to -0.7)
PlGF result at first testing			
PlGF <12	117 (29.5)	69 (24.0)	
PlGF 12-100	136 (34.3)	97 (33.8)	
PlGF >100	144 (36.3)	121 (42.2)	

Table 2: Maternal and perinatal adverse outcomes for women in MAPPLE (revealed PlGF testing) and PELICAN (concealed PlGF testing) cohort studies presenting prior to 35 weeks' gestation with comparisons for major outcomes.

	MAPPLE (revealed PlGF testing)	PELICAN (concealed PlGF testing);	Risk ratio
	n=396	**n=287**	
Final diagnosis of pre-eclampsia (n, %)	193 (52.9)	176 (61.3)	0.86 (0.75 to 0.99)
Women with maternal adverse outcomes (n, %)	47 (11.9)	29 (10.1)	1.17 (0.76 to 1.82)
Maternal adverse outcomes (non-exclusive) (n)	55	36	-
Maternal death	0	0	-
Central nervous system			
Eclampsia	0	1	-
Stroke; hypertensive encephalopathy	0	0	-
Cortical blindness or retinal detachment	0	0	-
Cardiovascular/ respiratory			
Myocardial infarction	0	0	-
Intubation (other than for caesarean section)	0	1	-
Pulmonary oedema	2	2	-
Haematological			
Platelets <50×10^9/L (without transfusion)	2	2	-
Disseminated intravascular coagulation	1	1	-
Thrombotic thrombocytopenic purpura/ haemolytic uraemic syndrome	0	0	-
Hepatic			
Dysfunction (Alanine transaminase ≥70IU/L)	38	23	
Haematoma; rupture; acute fatty liver of pregnancy	1	0	-
Renal			
Creatinine >150 µmol/L	7	2	-
Dialysis	2	0	-
Obstetric			
Placental abruption	1	4	-
Number of infants	**n=433**	**n=299**	**Risk Ratio**
Infants with composite perinatal adverse outcome (perinatal death or neonatal adverse outcome) (n, %)	131 (30.4)	60 (20.1)	1.51 (1.15 to 1.98)
Perinatal death (n, %)	2 (0.5)	9 (3.0)	0.16 (0.03 to 0.74)
Stillbirth (n, %)	1 (0.2)	7 (2.3)	-
Early neonatal death (n, %)	1 (0.2)	2 (0.7)	-
Infants with neonatal adverse outcomes (n, %)	131 (30.4)	51 (17.1)	1.78 (1.32 to 2.41)
Neonatal adverse outcomes (non-exclusive) (n)	178	62	-
Respiratory distress syndrome (n)	128 (30.5)	46 (15.4)	-

Bronchopulmonary dysplasia (n)	28 (6.7)	6 (2.0)	-
Intraventricular haemorrhage (Grade 3 or 4) (n)	4 (0.9)	0 (0.0)	-
Necrotising enterocolitis (n)	7 (1.7)	4 (1.3)	-
Retinopathy of prematurity (n)	11 (2.6)	6 (2.0)	-
Infants admitted to neonatal unit (n, %)	190 (45.5)	117 (39.8)	1.14 (0.95 to 1.37)

Table 3: Impact of PLGF testing of the pregnancy management in women in MAPPLE (revealed PlGF testing) and PELICAN (concealed PlGF testing) cohort studies presenting prior to 35 weeks' gestation

	MAPPLE (revealed PlGF testing)	PELICAN (concealed PlGF testing)	Median Difference/ Risk Ratio
Maternal	**n=397**	**n=287**	
Interval from first test to delivery (days; median, quartiles)	24 (4 to 52)	29 (11 to 59)	-6.0 (-2.0 to -10.0)
Antenatal steroids (n, %)	236 (59.9)	88 (30.7)	1.95 (1.61 to 2.37)
Induction of labour (n, %)	97 (24.5)	108 (37.6)	0.66 (0.52 to 0.82)
Fetal	**n=433**	**n=299**	
Ultrasound scans (n, %)	384 (89.1)	295 (98.7)	0.90 (0.87 to 0.94)
Estimated fetal weight <10th centile (n/N, %)	80/375 (21.3)	83/285 (29.1)	0.73 (0.56 to 0.96)
Absent or reduced end diastolic flow (umbilical artery Doppler (n/N, %)	52/384 (13.5)	37/285 (13.1)	1.04 (0.70 to 1.54)
Perinatal	**n=433**	**n=299**	
Gestational age at delivery (weeks; median, quartiles)	34.9 (32.0-37.1)	36.7 (33.6–38.6)	-1.4 (-0.9 to -2.0)
Caesarean section (n, %)	318 (73.8)	193 (64.5)	1.14 (1.03 to 1.26)
Birthweight (grams; median, quartiles)	2280 (1490-2960)	2420 (1620–3125)	-160 (-15 to -310)
Small for gestational age infant <10th centile (n, %)	181 (42.2)	145 (48.5)	0.87 (0.74 to 1.02)
Small for gestational age infant <3rd centile (n, %)	124 (28.9)	108 (36.1)	0.80 (0.65 to 0.99)

Table 4: Maternal and fetal outcomes in women in MAPPLE (revealed PlGF testing) and PELICAN (concealed PlGF testing) cohort studies presenting prior to 35 weeks' gestation presented by PlGF results at enrolment.

	MAPPLE (revealed)	PELICAN (concealed)	MAPPLE (revealed)	PELICAN (concealed)	MAPPLE (revealed)	PELICAN (concealed)
	PlGF <12	**PlGF <12**	**PlGF 12-100**	**PlGF 12-100**	**PlGF >100**	**PlGF >100**
Maternal	**n=116**	**n=69**	**n=137**	**n=97**	**n=143**	**n=121**
Final diagnosis of pre-eclampsia (n, %)	51 (48.6)	67 (97.1)	69 (53.1)	72 (74.2)	73 (56.2)	37 (30.6)
Women with any maternal adverse outcome (n, %)	25 (21.6)	12 (17.4)	16 (11.7)	8 (8.2)	6 (4.2)	9 (7.4)
Eclampsia	0	0	0	1	0	0
Intubation	0	1	0	0	0	0
Pulmonary oedema	1	2	1	0	0	0
Platelets $<50\times10^9$/L	2	1	1	0	0	1
Disseminated intravascular coagulation	1	1	0	0	0	0
Dysfunction (Alanine transaminase ≥70IU/L)	23	9	11	7	4	7
Creatinine >150 µmol/L	1	2	4	0	2	0
Dialysis	0	0	1	0	1	0
Placental abruption	1	3	0	0	0	1
Interval from first test to delivery (median, quartiles)	3 (1 to 13)	9 (3 to 16)	19 (6 to 43)	23 (11 to 40)	48 (32 to 69)	61 (37 to 90)
Antenatal steroids for fetal lung maturity (n, %)	103 (89.6)	41 (59.4)	81 (59.6)	34 (35.1)	52 (36.4)	13 (10.7)
Induction of labour (n, %)	10 (8.6)	13 (18.8)	35 (25.5)	44 (45.4)	52 (36.4)	51 (42.1)
Antenatal clinic or assessment unit visits (mean, SD)	2.5 (5.5)	N/A	3.7 (5.3)	N/A	5.2 (5.5)	N/A
Antenatal inpatient nights (mean, SD)	2.3 (4.8)	N/A	2.4 (5.8)	N/A	3.8 (5.7)	N/A
Fetal	**n=122**	**n=69**	**n=158**	**n=105**	**n=151**	**n=125**
Number with ultrasound scans (n, %)	111 (91.0)	68 (98.6)	146 (92.4)	104 (98.4)	127 (84.1)	123 (90.6)
Estimated fetal weight <10th centile (n/N, %)	50/109 (45.9)	43/68 (63.2)	17/142 (12.0)	28/99 (28.3)	13/124 (10.5)	12/118 (10.2)
Absent or reduced end diastolic flow in umbilical artery - Doppler (n/N, %)	36/111 (32.4)	24/68 (35.3)	12/146 (8.2)	9/99 (9.1)	4/127 (3.1)	4/118 (3.4)

Table 5: Perinatal outcomes in MAPPLE (revealed PlGF testing) and PELICAN (concealed PlGF testing) cohort studies presenting prior to 35 weeks' gestation presented by PlGF results at enrolment.

	MAPPLE (revealed)	PELICAN (concealed)	MAPPLE (revealed)	PELICAN (concealed)	MAPPLE (revealed)	PELICAN (concealed)
	PlGF <12	**PlGF <12**	**PlGF 12-100**	**PlGF 12-100**	**PlGF >100**	**PlGF >100**
Perinatal	**n=124**	**n=69**	**n=158**	**n=105**	**n=151**	**n=125**
Stillbirth (n, %)	1 (0.8)	4 (5.8)	0	3 (2.9)	0	0
Neonatal death (n, %)	1 (0.8)	2 (2.9)	0	0	0	0
Gestational age at delivery (weeks; median, quartiles)	31.2 (29.0-33.4)	31.9 (29.3-34.1)	35.0 (33.3-36.8)	35.7 (34.1-37.9)	37.4 (36.1-38.4)	38.4 (37–39.9)
Delivery <37 weeks (n, %)	120 (100)	65 (94.2)	126 (79.7)	64 (60.1)	58 (38.4)	29 (23.2)
Delivery <34 weeks (n, %)	97 (80.8)	50 (72.5)	48 (30.4)	23 (21.9)	22 (14.6)	10 (8.0)
Caesarean section (n, %)	115 (94.3)	57 (82.6)	120 (75.9)	74 (70.5)	83 (55.0)	62 (49.6)
Birthweight (grams; mean, SD)	1360 (970-1650)	1280 (862-1678)	2290 (1810-2740)	2270 (1757-2830)	2990 (2590-3355)	3100 (2672-3505)
Small for gestational age infant <10th centile (n, %)	92 (76.7)	57 (82.6)	65 (41.1)	59 (56.2)	24 (15.9)	29 (23.2)
Small for gestational age infant <3rd centile (n, %)	71 (59.2)	50 (72.5)	44 (27.8)	46 (43.8)	9 (6.0)	12 (9.6)
Neonatal unit admission (n, %)	94 (81.7)	53 (82.8)	71 (46.4)	46 (43.8)	25 (16.7)	18 (14.4)
Infants with neonatal adverse outcomes (n, %)	74 (60.7)	27 (39.1)	37 (23.4)	14 (13.3)	20 (13.2)	10 (8.0)
Respiratory distress syndrome (n, %)	72 (62.1)	23 (33.3)	36 (23.4)	14 (13.3)	20 (13.3)	9 (7.2)
Bronchopulmonary dysplasia (n, %)	19 (16.4)	6 (8.7)	4 (2.6)	0	5 (3.3)	0
Intraventricular haemorrhage (Grade 3/4) (n, %)	2 (1.6)	0	2 (1.3)	0	0	0
Necrotising enterocolitis (n, %)	4 (3.4)	3 (4.3)	2 (1.3)	0	1 (0.7)	1 (0.8)
Retinopathy of prematurity (n, %)	7 (6.0)	5 (7.2)	3 (1.9)	1 (1.0)	1 (0.7)	0

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